# **PCT**

#### ORLD INTELLECTUAL PROPERTY ORGANIZA International Bureau



#### INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7:

A61K 31/00

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WO 00/16755

A2

(43) International Publication Date:

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17 September 1999 (17.09.99)

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9820420.9

18 September 1998 (18.09.98) GB

(71) Applicant (for all designated States except US): GLAXO GROUP LIMITED [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(72) Inventors; and

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- (74) Agent: TEUTEN, Andrew, J.; Glaxo Wellcome plc, Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

#### Published

Without international search report and to be republished upon receipt of that report.

- (54) Title: ANTIVIRAL COMBINATIONS
- (57) Abstract

The present invention relates to therapeutic combinations comprising (2R, cis) -4-amino-1- (2-hydroxymethyl-1, 3-oxathiolan-5-yl) -pyrimidin-2-one (lamivudine) and a second therapeutic agent selected from (9-[(R) -2-(phosphonomethoxy) ethyl]adenine, (PMEA or adefovir) and bis(pivaloyloxymethyl) (9-[(R) -2- (phosphonomethoxy)ethyl]adenine, (the oral prodrug of PMEA, adefovir dipivoxil) w hich have anti-hepatitis B virus (HBV) activity. The present invention is also concerned with pharmaceutical compositions containing said combinations and their use in the treatment of HBV infections including infections with HBV mutants bearing resistance to nucleoside and/or non-nucleoside inhibitors.

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A61K 31/505, 31/52

A3

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18 September 1998 (18.09.98) GB

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#### Published

With international search report.

GN, GW, ML, MR, NE, SN, TD, TG).

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC,

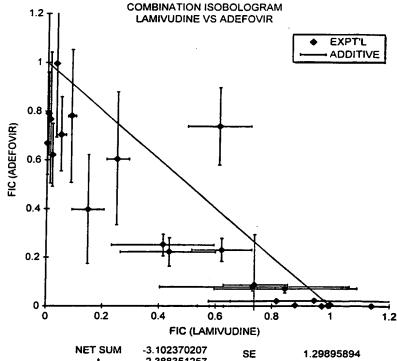
NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA,

(88) Date of publication of the international search report:
25 May 2000 (25.05.00)

(54) Title: ANTIVIRAL COMBINATIONS OF LAMIVUDINE AND ADEFOVIR

#### (57) Abstract

The present invention relates to therapeutic combinations comprising (2R, cis) -4-amino-1- (2-hydroxymethyl-1, 3-oxathiolan-5-yl) -pyrimidin-2-one (lamivudine) and a second therapeutic agent selected from (9-[(R) -2-(phosphonomethoxy) ethyl]adenine, (PMEA or adefovir) and bis(pivaloyloxymethyl) (9-[(R) -2-(phosphonomethoxy)ethyl]adenine, (the oral prodrug of PMEA, adefovir dipivoxil) w hich have anti-hepatitis B virus (HBV) activity. The present invention is also concerned with pharmaceutical compositions containing said combinations and their use in the treatment of HBV infections including infections with HBV mutants bearing resistance to nucleoside and/or non-nucleoside inhibitors.



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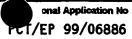
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ional Application No PCT/EP 99/06886

A CLASSIF	CATION OF SUBJECT MATTER A61K31/505 A61K31/52			
110 /	VOTESTA 202 VOTESTA 25	•	]	
According to	International Patent Classification (IPC) or to both national classification	on and IPC		
B. FIELDS S	BEARCHED			
Minimum doc	currentation searched (classification system followed by classification $\Delta 6.1\mathrm{K}$	n symbols)		
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Electronic da	ata base consulted during the international search (name of data base	e and, where practical, search terms used)		
C. DOCUME	ENTS CONSIDERED TO BE RELEVANT			
Category °	Citation of document, with indication, where appropriate, of the rele	vant passages	Relevant to claim No.	
X,P	BARTNOF H. S.: "Preveon shows be for patients co-infected with HIV HIV AND HEPATITIS.COM, 'Online! 18 August 1999 (1999-08-18), XPOO Retrieved from the Internet: <url:http: 0089904.html="" www.hivandhepatitis.c=""> 'retrieved on 2000-the whole document</url:http:>	and HBV" 2132867 om/hiv/v1	1–21	
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		Y Patent family members are listed	In annex	
X Fur	ther documents are listed in the continuation of box C.	X Patent family members are listed		
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consi	nent defining the general state of the art which is not idened to be of particular relevance	cited to understand the principle or the invention	neory underlying the	
filing		"X" document of particular relevance; the cannot be considered novel or canno involve an inventive step when the d	nt de considered to	
which is cited to establish the publication date of another  "Y" document of particular relevance; the claimed invention  chation or other special reason (as specified)				
"O" document referring to an oral disclosure, use, exhibition or document is combined with one or more other such document is combined with one or more other such document is combined with one or more other such document is combined with one or more other such document is combined with one or more other such document is combined with one or more other such document is combined with one or more other such document is combined with one or more other such document is combined with one or more other such document.				
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Date of the	e actual completion of the international search	Date of mailing of the international s	earch report	
	13 March 2000	27/03/2000		
Name and	I mailing address of the ISA European Patent Office, P.B. 5818 Patentiaan 2	Authorized officer		
	NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo ni, Fax: (+31-70) 340-3016	Gonzalez Ramon,	N	

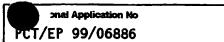
onal Application No PCT/EP 99/06886

C (Continue	(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT				
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.			
X,P	PERRILLO: "Gilead Presents Preliminary Clinical Data demostrating activity of adefovir dipivoxil against lamivudine-resistant Hepatitis B virus" GILEAD SCIENCES PRESS RELEASE ARCHIVE, 'Online! 9 April 1999 (1999-04-09), XP002132868 Retrieved from the Internet: <url:http: frame_home.php3="" webpage_templates="" www.gilead.com=""> 'retrieved on 2000-03-13! the whole document</url:http:>	1-21			
X, P	THOMPSON M. ET AL: "Randomized Study of Adefovir Dipivoxil (ADV) in combination with Indinavir (IDV) and reverse transcriptase inhibitors for treatment-naive HIV infected patients" ABSTRACTS AND POSTERS IAPAC, 'Online! 8 November 1998 (1998-11-08), XP002132869 Retrieved from the Internet: <url:http: conferences="" gileadglasgow5.html="" glasgow98="" www.iapac.org=""> 'retrieved on 2000-03-13! abstract; table 1</url:http:>	1-21			
X	ONO-NITA, S. K. (1) ET AL: "Susceptibility of lamivudine resistant hepatitis B virus to other antivirals: Adefovir and lobucavir." HEPATOLOGY, (OCT., 1998) VOL. 28, NO. 4 PART 2, PP. 165A. MEETING INFO.: BIENNIAL SCIENTIFIC MEETING OF THE INTERNATIONAL ASSOCIATION FOR THE STUDY OF THE LIVER AND THE 49TH ANNUAL MEETING AND POSTGRADUATE COURSES OF THE AMERICAN ASSOCIATION FOR THE , XP000890075 abstract	1-21			
X	MULATO, A.S. ET AL: "Anti-HIV activity of adefovir (PMEA) and PMPA in combination with antiretroviral compounds: in vitro analyses" ANTIVIRAL RES. (1997), 36(2), 91-97, XP000890091 abstract; figure 1A page 93, column 2, paragraph 2  -/	1-21			



	PCT/EP 99/06886
ation) DOCUMENTS CONSIDERED TO BE RELEVANT	
Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
SHAW, T. ET AL: "Synergistic inhibition of in vitro hepadnaviral replication by PMEA and penciclovir or lamivudine." ANTIVIRAL RESEARCH, (1997) VOL. 34, NO. 2, PP. A51. MEETING INFO.: MEETING OF THE INTERNATIONAL SOCIETY FOR ANTIVIRAL RESEARCH AND THE TENTH INTERNATIONAL CONFERENCE ON ANTIVIRAL RESEARCH ATLANTA, GEORGIA, USA APRIL 6-11, 1997, XP000890096 abstract	1-21
DE CLERCQ E: "Perspectives for the treatment of hepatitis B virus infections." INTERNATIONAL JOURNAL OF ANTIMICROBIAL AGENTS, (1999 JUL) 12 (2) 81-95. REF: 72, XP000890077 abstract; figure 3 page 92, column 2	1-21
PESSOA M.G. ET AL: "Update on clinical trials in the treatment of hepatitis B." JOURNAL OF GASTROENTEROLOGY AND HEPATOLOGY, (1999) 14/SUPPL. (S6-S11)., XP000890090 abstract page S10, column 2	1–21
PETERS M G ET AL: "Fulminant hepatic failure resulting from lamivudine -resistant hepatitis B virus in a renal transplant recipient: durable response after orthotopic liver transplantation on adefovir dipivoxil and hepatitis B immune globulin."  TRANSPLANTATION, (1999 DEC 27) 68 (12) 1912-4., XP000890081 abstract; table 1	1-21
WO 99 66936 A (NOVIRIO PHARMACEUTICALS LIMITE; BRYANT MARTIN L; MYERS MAUREEN W () 29 December 1999 (1999-12-29) claims 11,12,38	1-22
	SHAW, T. ET AL: "Synergistic inhibition of in vitro hepadnaviral replication by PMEA and penciclovir or lamivudine." ANTIVIRAL RESEARCH, (1997) VOL. 34, NO. 2, PP. A51. MEETING INFO.: MEETING OF THE INTERNATIONAL SOCIETY FOR ANTIVIRAL RESEARCH AND THE TENTH INTERNATIONAL CONFERENCE ON ANTIVIRAL RESEARCH ATLANTA, GEORGIA, USA APRIL 6-11, 1997, XP000890096 abstract  DE CLERCQ E: "Perspectives for the treatment of hepatitis B virus infections." INTERNATIONAL JOURNAL OF ANTIMICROBIAL AGENTS, (1999 JUL) 12 (2) 81-95. REF: 72, XP000890077 abstract; figure 3 page 92, column 2  PESSOA M.G. ET AL: "Update on clinical trials in the treatment of hepatitis B." JOURNAL OF GASTROENTEROLOGY AND HEPATOLOGY, (1999) 14/SUPPL. (S6-S11)., XP000890090 abstract page S10, column 2  PETERS M G ET AL: "Fulminant hepatic failure resulting from lamivudine -resistant hepatitis B virus in a renal transplant recipient: durable response after orthotopic liver transplantation on adefovir dipivoxil and hepatitis B immune globulin." TRANSPLANTATION, (1999 DEC 27) 68 (12) 1912-4., XP000890081 abstract; table 1  WO 99 66936 A (NOVIRIO PHARMACEUTICALS LIMITE; BRYANT MARTIN L; MYERS MAUREEN W () 29 December 1999 (1999-12-29)





		·	PCT/EP 99/0688		99/06886
Patent document ited in search repo	nt	Publication date	Patent family member(s)		Publication date
10 9966936	A	29-12-1999	NONE		
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PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To: GLAXO WELLCOME PLC Glaxo Wellcome House

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

Attn. Teuten, Andrew J. Berkeley Avenue Greenford Middlesex UB6 ONN UNITED KINGDOM	(PCT Rule 44.1)			
	Date of mailing (day/month/year) 27/03/2000			
Applicant's or agent's file reference				
PU3514/PCT	FOR FURTHER ACTION See paragraphs 1 and 4 below			
International application No.	International filing date			
PCT/EP 99/06886	(day/month/year) 17/09/1999			
Applicant GLAXO GROUP LIMITED et al.				
The applicant is hereby notified that the International Search Filing of amendments and statement under Article 19: The applicant is entitled, if he so wishes, to amend the claim When? The time limit for filing such amendments is normal	s of the International Application (see Rule 46):			
Where? Directly to the international Bureau of WIPO 34, chemin dee Colombettes 1211 Geneva 20, Switzerland Fascimile No.: (41–22) 740.14.35	20 MAR 2000 WIT			
2. The applicant is hereby notified that no international Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.				
applicant's request to forward the texts of both the prot	n transmitted to the international Bureau together with the lest and the decision thereon to the designated Offices.			
no decision has been made yet on the protest; the app	licant will be notified as soon as a decision is made.			
4. Further action(s): The applicant is reminded of the following:				
Shortly after 18 months from the priority date, the international application will be published by the international Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the international Bureau as provided in Rules 90 <i>bis</i> .1 and 90 <i>bis</i> .3, respectively, before the completion of the technical preparations for international publication.				
Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).				
Within 20 months from the priority date, the applicant must perfor before all designated Offices which have not been elected in the priority date or could not be elected because they are not bound	e demand or in a later election within 19 months from the			
Name and mailing address of the International Searching Authority	Authorized officer			
European Patent Office, P.B. 5818 Patentlaan 2  NL-2280 HV Rijswijk  Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Claudia Aragone			

Form POT/104.000 (July 1008)

#### NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

#### **INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19**

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international pbulication. Furthermore, it should be emphasized that provisional protection is available in some States only.

#### What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

#### When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

#### Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been his word, see below.

#### How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

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A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

#### What d cuments must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

#### NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

# The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

- [Where originally there were 48 claims and after amendment of some claims there are 51]:
   "Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
- [Where originally there were 15 claims and after amendment of all claims there are 11]: "Claims 1 to 15 replaced by amended claims 1 to 11."
- [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
   "Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or "Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
- 4. [Where various kinds of amendments are made]: "Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

#### "Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

#### Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted; the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

#### Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

## PATENT COOPERATION TREATY

# **PCT**

### **INTERNATIONAL SEARCH REPORT**

(PCT Article 18 and Rules 43 and 44)

International application No.	Applicant's or agent's file reference  FOR FURTHER see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.  ACTION						
Applicant  GLAXO GROUP LIMITED et al.  This international Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the international Bureau.  This international Search Report consists of a total of		International filing date (day/month/year)	(Earliest) Priority Date (day/month/year)				
This international Search Report has been prepared by this international Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the international Bureau.  This international Search Report consists of a total of	PCT/EP 99/06886	PCT/EP 99/ 06886 17/09/1999 18/09/1998					
The International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.    Trills International Search Report consists of a total of		<del> </del>					
This international Search Report consists of a total of	GLAXO GROUP LIMITED et al	•					
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International Application No PCT/EP 99/06886

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	ENTS CONSIDERED TO BE RELEVANT	<u> </u>
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	BARTNOF H. S.: "Preveon shows benefits	1.21
A, r	for patients co-infected with HIV and HBV"	1-21
	HIV AND HEPATITIS.COM, 'Online!	
	18 August 1999 (1999-08-18), XP002132867	
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X Fur	ther documents are listed in the continuation of box C.  Patent family members are	listed in annex.
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.• 	NL - 2280 HV Rijswijk	
ı	Fax: (+31-70) 340-3016 Gonzalez Ramon	, N

PCT/EP 99/06886

Category *	ation) DOCUMENTS CONSIDERED TO BE RELEVANT  Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	PERRILLO: "Gilead Presents Preliminary Clinical Data demostrating activity of adefovir dipivoxil against lamivudine-resistant Hepatitis B virus" GILEAD SCIENCES PRESS RELEASE ARCHIVE, 'Online! 9 April 1999 (1999-04-09), XP002132868 Retrieved from the Internet: <url:http: es="" frame_home.php3="" webpage_templat="" www.gilead.com=""> 'retrieved on 2000-03-13! the whole document</url:http:>	1-21
X,P	THOMPSON M. ET AL: "Randomized Study of Adefovir Dipivoxil (ADV) in combination with Indinavir (IDV) and reverse transcriptase inhibitors for treatment-naive HIV infected patients" ABSTRACTS AND POSTERS IAPAC, 'Online! 8 November 1998 (1998-11-08), XP002132869 Retrieved from the Internet: <url:http: conferences="" gileadglasgow5.html="" glasgow98="" www.iapac.org=""> 'retrieved on 2000-03-13! abstract; table 1</url:http:>	1-21
<b>X</b>	ONO-NITA, S. K. (1) ET AL: "Susceptibility of lamivudine resistant hepatitis B virus to other antivirals: Adefovir and lobucavir." HEPATOLOGY, (OCT., 1998) VOL. 28, NO. 4 PART 2, PP. 165A. MEETING INFO.: BIENNIAL SCIENTIFIC MEETING OF THE INTERNATIONAL ASSOCIATION FOR THE STUDY OF THE LIVER AND THE 49TH ANNUAL MEETING AND POSTGRADUATE COURSES OF THE AMERICAN ASSOCIATION FOR THE, XP000890075 abstract	1-21
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International Application No PCT/EP 99/06886

C.(Continu	ation) DOCUMENTS CONSIDERED TO BE RELEVANT	
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SHAW, T. ET AL: "Synergistic inhibition of in vitro hepadnaviral replication by PMEA and penciclovir or lamivudine." ANTIVIRAL RESEARCH, (1997) VOL. 34, NO. 2, PP. A51. MEETING INFO.: MEETING OF THE INTERNATIONAL SOCIETY FOR ANTIVIRAL RESEARCH AND THE TENTH INTERNATIONAL CONFERENCE ON ANTIVIRAL RESEARCH ATLANTA, GEORGIA, USA APRIL 6-11, 1997, XP000890096 abstract	1-21
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Information on patent family members

International Application No PCT/EP 99/06886

Patent document cited in search repor	t .	Publication date	Patent family member(s)	Publication date	
W0 9966936	A	29-12-1999	NONE		

# PATENT COOPERATION TREATY

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International application No. PCT/EP99/06886	Applicant's or agent's file reference PU3514/PCT
International filing date (day/month/year)	Priority date (day/month/year)
17 September 1999 (17.09.99)	18 September 1998 (18.09.98)
Applicant	
BROWN, Nathaniel, A. et al	
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was not made before the expiration of 19 months from the pri	ority date or, where Rule 32 applies, within the time limit under
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# REQUEST

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The undersigned requests that the present International application be processed according to the Patent Cooperation Treaty	International Filing Drie  1 7 SEP 1999 (17. 09. 1999)  EUROPEAN PATENT OFFICE PCT INTERNATIONAL APPLICATION Name of receiving Office and "PCT International Application"  Applicant's or agent's file reference (if desired) (12 characters maximum) PU3514/PCT
Box No. I TITLE OF INVENTION	to the constitution of the
Antiviral C	combinations
Box No. II APPLICANT	
Name and address: (Family name followed by given name; for a legal en designation. The address must include postal code and name of country. The indicated in this Box is the applicant's State (that is, country) of residence if rindicated below).  Glaxo Group Limited Glaxo Wellcome House Berkeley Avenue Greenford, Middlesex UB6 ONN, GB  State (i.e. country) of nationality:	This person is also inventor.  Telephone No. 0171 493 4060  Facsimile No. 0181 966 8838  Teleprinter No. 25456
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This person is applicant all designated all designated States for the purposes of:  all designated States of the United States of the U	es except the United States the States indicated in the
Box No. III FURTHER APPLICANTS AND/OR (FURTHE	
Name and address: (Family name followed by given name; for a legal enti- designation. The address must include postal code and name of country. The indicated in this Box is the applicant's State (that is, country) of residence if no indicated below.)  BROWN, Nathaniel A.  Glaxo Wellcome Inc.  Five Moore Drive  Aesearch Triangle Park  NC 27709  US	country of the address This
	State (i.e. country) of residence:
This person is applicant all designated all designated States for the purposes of: States the United States of Further applicants and/or (further) inventors are indicated on a	America of America only the Supplemental Box
Box No. IV AGENT OR COMMON REPRESENTATIVE;	OR ADDRESS FOR CORRESPONDENCE
The person identified below is hereby/has been appointed to act on both the applicant(s) before the competent International Authorities as:	ehalf agent common representative
Name and address: (Family name followed by given name; for a legal ent designation. The address must include postal code an IEUTEN, Andrew J. Glaxo Wellcome plc Glaxo Wellcome House, Berkeley Avenue	ity, full official
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Name and address: (Family name followed by given name; for a logid entity, full official designation that Bas is the applicant in State that is, country) of residence; if no State of residence is unknowed below.)  Grave Wellcome Inc.  Five Moore Drive  Research Triangle Park  NC 27709  US  State (i.e. country) of nationality:  This person is:	TOTAL CONTINUE OF THE PROPERTY
This person is applicant and inventor inventor only (if this cheeck-box is marked. do not fill in below.)  State (i.e. country) of nationality:  GRAY, Douglas Fraser Glaxo Wellcome ple GB State (i.e. country) of nationality:  GRAY, Douglas Fraser Glaxo Wellcome ple GB State (i.e. country) of nationality:  State (i.e. country) of natio	
Research Triangle Park  NC 27709  US  State (i.e. country) of nationality:  US  This person is applicant for the purposes of:  State (i.e. country) of nationality:  US  This person is applicant in all designated states except the United States indicated in the State in the country of residence:  US  The address must include prestud code and name of country. The country of the address indicated in the State indicated below.)  GRAY, Douglas Fraser Glaxo Wellcome plc  GB  This person is applicant and inventor inventor only (if this check-box is marked, do not fill in below.)  State (i.e. country) of nationality:  GB  This person is applicant in the state indicated in the State i	The dutiess must include postal code and name of country. The country of the address indicated in this  Bax is the applicant's State (that is, country) of residence if no State of residence is indicated below.)  CONDREAY, Lynn D.  Glaxo Wellcome Inc.
This person is applicant only states and address: (Family name followed by given name; for a legal entity, full official designation of America only of residence:  GRAY, Douglas Fraser (Glaxo Wellcome plc split of the United States of America only of residence:  GRAY, Douglas Fraser (Glaxo Wellcome plc split of the United States of America only of the address materials and inventor inventor only (If this check-box is marked, do not fill in below.)  GRAY, Douglas Fraser (Glaxo Wellcome plc split of the United States of America only of residence:  GB This person is applicant only applicant and inventor inventor only (If this check-box is marked, do not fill in below.)  GB State (i.e. country) of residence:  GB This person is applicant only applicant only of the during the country of the address materials of the United States of America only is applicant only applicant only applicant only applicant only applicant only of the states indicated in the state of the United States of America only (If this check-box is marked, do not fill in below.)  This person is applicant only	Research Triangle Park NC 27709 US
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Glaxo Wellcome plc  891-995 Greenford Road  Greenford, Middlesex, UB6 0HE  GB  This person is applicant  all designated States occept the United States of America  The address must include postal code and name of country. The country of mationality:  US  State (i.e. country) of nationality:  This person is applicant all designated States of America  The address must include postal code and name of country. The country of the address indicated below.)  State (i.e. country) of nationality:  State (i.e. country) of nationality:  US  This person is applicant and inventor only (If this check-box is marked, do not fill in below.)  State (i.e. country) of residence:  US  This person is applicant and inventor inventor only (If this check-box is marked, do not fill in below.)  State (i.e. country) of nationality:  This person is applicant and inventor inventor only (If this check-box is marked, do not fill in below.)  State (i.e. country) of residence:  US  This person is applicant and inventor inventor only (If this check-box is marked, do not fill in below.)  State (i.e. country) of residence:  US  This person is applicant and inventor inventor only (If this check-box is marked, do not fill in below.)  State (i.e. country) of residence:  US  This person is applicant and inventor inventor only (If this check-box is marked, do not fill in below.)  State (i.e. country) of nationality:  State (i.e. country) of residence:  US  This person is inventor only (If this check-box is marked, do not fill in below.)  State (i.e. country) of nationality:  State (i.e. country) of residence:  This person is inventor only (If this check-box is marked, do not fill in below.)  This person is:  This person is:  This person is:  The States indicated in this person is marked, do not fill in below.)  This person is:  The State (i.e. country) of nationality:  State (i.e. country) of residence:  This person is applicant and inventor inventor only (If this check-box is marked, do not fill in below.)  This person is applicant and inventor invent	Name and address: (Family name followed by given name; for a legal entity, full official designation.  The address must include postal code and name of country. The country of the address indicated in this  Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)  This person is:
State (i.e. country) of nationality:  GB  State (i.e. country) of residence:  GB  This person is applicant   salt designated   salt designation   salt designated   salt designated   salt designation   salt designation   salt designated   salt designated   salt designation	Glaxo Wellcome plc  891-995 Greenford Road  Greenford, Middlesex,  applicant and inventor inventor only (If this check-box is marked, do not fill in below.)
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Name and address: (Family name followed by given name; for a legal entity, full official designation The address must include postal code and name of country. The country of the address indicated in this Bax is the applicant is State (that is, country) of residence if no State of residence is indicated below.)  RUBIN, Marc Glaxo Wellcome Inc.  Tive Moore Drive Research Triangle Park NC 27709  US This person is applicant  I designated all designated all designated States except to the United States of America only of America only of the States indicated in this Bax is the applicant's State (that is, country) of residence:  This person is applicant  I designated of residence is indicated below.)  State (i.e. country) of nationality:  US This person is applicant all designated the States of America only of America only of America only of America only of Presidence:  The address must include postal code and name of country. The country of the address must include postal code and name of country. The country of the address must include the postal code and name of country. The country of the address must include postal code and name of country. The country of the address must include postal code and name of country. The country of the address must include in this Bax is the applicant's State (that is, country) of residence is indicated below.)  State (i.e. country) of nationality:  State (i.e. country) of nationality:  State (i.e. country) of residence:  This person is applicant and inventor inventor only (If this check-box is marked, do not fill in below.)  This person is applicant and inventor inventor only (If this check-box is marked, do not fill in below.)  The States indicated in the Surplemental Box the United States of America only of America	for the purposes of:  States
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Research Triangle Park  NC 27709  US  State (i.e. country) of nationality:  US  This person is applicant for the purposes of:  Name and address: (Family name followed by given name; for a legal entity, full official designation.  The address must include postal code and name of country. The country of the address indicated in this  Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)  State (i.e. country) of nationality:  State (i.e. country) of residence:  This person is applicant and inventor inventor only (If this check-box is marked, do not fill in below.)  State (i.e. country) of residence:  This person is applicant  all designated all designated States except the United States of America only the States indicated in the Supplemental Box  The person is applicant and inventor inventor only (If this check-box is marked, do not fill in below.)  Further applicants and/or (further) inventors are indicated on a continuation sheet.	Glaxo Wellcome Inc.    Applicant and inventor
This person is applicant   all designated   states except   the United States of America only   the States indicated in the Supplemental Box    Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant 's State (that is, country) of residence if no State of residence is indicated below.)  State (i.e. country) of nationality:  State (i.e. country) of residence:  This person is applicant   all designated   all designated States except   the United States   the States indicated in the States indicated in the States indicated in the United States of America   the United States   the States indicated in the States indicated in the States indicated in the States indicated in the United States   the United States   the States indicated in the United States   the United States   the States indicated in the United States of America only   the States indicated in the	Research Triangle Park NC 27709 US
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form PC 1 (PC)/1111 (continuation cheet) (July 1009)	Further applicants and/or (further) inventors are indicated on a continuation sheet.  Form PCT/RO/101 (continuation sheet) (July 1998)

See Notes to the request form

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Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).								
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	Box No. V DESIGNATION OF STATES										
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Precautio	Dary Designation Statements In addition of the										

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)

#### PATENT COOPERATION TREATY

From the INTERNATIONAL PRELIMINAR	RY EXAMINING AUTHORITY	Property	
To: Teuten, Andrew J. GLAXO WELLCOME PLC Glaxo Wellcome House Berkeley Avenue Greenford Middlesex UB6 0NN GRANDE BRETAGNE	Global Intellectual  RECEIVED \$ OCT 20	00 VOTFIC	PCT  ATION OF TRANSMITTAL OF TERNATIONAL PRELIMINARY XAMINATION REPORT  (PCT Rule 71.1)  09.10:2000
Applicant's or agent's file reference PU3514/PCT		ı	MPORTANT NOTIFICATION
International application No. PCT/EP99/06886	International filing date (d 17/09/1999	lay/month/year)	Priority date (day/month/year) 18/09/1998
Applicant GLAXO GROUP LIMITED et	al.		

- 1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
- 2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
- 3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

#### 4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/

European Patent Office D-80298 Munich

Tel. +49 89 2399 - 0 Tx 523656 epmu d

Fax. 440 99 2899 - 4465

**Authorized officer** 

Oberhauser, A

Tel +49 89 2399-8139



# **TENT COOPERATION TR**

# PCT

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference		See Notification of Transmittal of International			
PU3514/PCT	FOR FURTHER ACTION	Preliminary Examination Report (Form PCT/IPEA/416)			
International application No.	International filing date (day/month	/year) Priority date (day/month/year)			
PCT/EP99/06886	17/09/1999	18/09/1998			
International Patent Classification (IPC) or	national classification and IPC				
A61K31/00					
Applicant					
GLAXO GROUP LIMITED et al.					
This international preliminary example and is transmitted to the applications.		by this International Preliminary Examining Authority			
2. This REPORT consists of a total	of 5 sheets, including this cover s	heet.			
been amended and are the		e description, claims and/or drawings which have containing rectifications made before this Authority ons under the PCT).			
These annexes consist of a total	of 3 sheets.				
		•			
3. This report contains indications i	elating to the following items:				
l ⊠ Basis of the report					
II □ Priority					
-	f opinion with regard to novelty, in	ventive step and industrial applicability			
IV ☐ Lack of unity of inve	ntion				
	t under Article 35(2) with regard to ations suporting such statement	novelty, inventive step or industrial applicability;			
VI   Certain documents	cited				
VII   Certain defects in th	e international application				
VIII   Certain observation	on the international application	•			
	. Data of	completion of this report			
Date of submission of the demand	Date of	completion of this report			
21/03/2000	09.10.2	000			
Name and mailing address of the internat	onal Authoriz	Authorized officer			
preliminary examining authority:  European Patent Office					
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Tel. +49 89 2399 - 0 Tx: 523 Fax: +49 89 2399 - 4465	· 1	one No. +49 89 2399 8599			



International application No. PCT/EP99/06886

### I. Basis of the report

١.	This report has been drawn on the basis of (substitute sheets which have been furnished to the receiving Office is response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.):								
	D s	cription, pages:							
	1-23	3	as originally filed						
	Clai	ms, No.:				•			
	1-22	2 .	as received on	25/08/2000	with letter of	25/08/2000			
	Dra	wings, No.:							
	1		as originally filed		·				
2.	The	amendments have	e resulted in the cancellation of:		•				
		the description,	pages:						
		the claims,	Nos.:						
		the drawings,	sheets:						
3.			een established as if (some of) the come of the disclosure as filed (F		 nts had not been made	e, since they have beer			
4.	Add	litional observation	s, if necessary:						
ill.	Nor	n-establishment o	f opinion with regard to novel	ty, inventive	step and industrial a	applicability			
			e claimed invention appears to lable have not been examined in		volve an inventive ste	ep (to be non-obvious),			
		the entire internat	ional application.						
	☒	claims Nos. 10-15	5,18-21.						
he	caus	·			•				



	Ø	the said international application, or the said claims Nos. 10-15,18-21 (see separate sheet, item 1) relate to the following subject matter which does not require an international preliminary examination (specify):								
		see separate sheet								
	<u> </u>	the description, claims or drawings (indicate particular elements below) or said claims Nos. are so unclear that no meaningful opinion could be formed (specify):								
	the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.									
		no international search i	eport h	as been e	established for the said claims Nos					
` <b>V</b> .					ith regard to novelty, inventive step or industrial upporting such statement					
1.	Sta	tement								
	No	velty (N)	Yes: No:	Claims Claims	1-21 (see separate sheet, items 3a and 3b) 22 (see separate sheet, item 3c)					
	Inv	entive step (IS)	Yes: No:	Claims Claims	1-9,11,19-21 (see separate sheet, item 3b) 10,12-18 (see separate sheet, item 3a)					
	Ind	lustrial applicability (IA)	Yes:	Claims	1-9,16-17,22 (YES; see separate sheet, item 2a); 10-15, 18-21 (see separate sheet, items 1 and 2b)					
			No:	Claims						
2	. Cit	ations and explanations								

see separate sheet

# The following IPER is based on the assumption that the present application is fully entitled to its priority date as claimed.

- Claims 10-15 and 18-21 relate to subject-matter considered by this Authority to be 1). covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).
- a). The subject-matter of claims 1-9, 16-17 and 22 fulfils the requirements of 2). industrial applicability.
  - b). For the assessment of the present claims 10-15 and 18-21 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.
- a). SHAW, T. ET AL: "Synergistic inhibition of in vitro hepadnaviral replication by 3). PMEA and penciclovir or lamivudine." ANTIVIRAL RESEARCH, (1997) VOL. 34, NO. 2, PP. A51. MEETING INFO.: MEETING OF THE INTERNATIONAL SOCIETY FOR ANTIVIRAL RESEARCH AND THE TENTH INTERNATIONAL CONFERENCE ON ANTIVIRAL RESEARCH ATLANTA, GEORGIA, USA APRIL 6-11, 1997 (=D1) discloses synergistic action of a combination of PMEA with lamivudine in ratios of 3:1 and 44:1 (see abstract). In the light of D1, the subjectmatter of claims 10,12-15, although formally novel since it relates to a treatment of a mammal, does not involve an inventive step since the synergistic action of PMEA with lamivudine is obvious from D1.

The same applies also to the subject-matter of claims 16-18 defining combinations of lamivudine with adefovir dipivoxil, since it is known from a further document D2 (=MULATO, A.S. ET AL: "Anti-HIV activity of adefovir (PMEA) and PMPA in combination with antiretroviral compounds: in vitro analyses" ANTIVIRAL RES. (1997), 36(2), 91-97) that adefovir dipivoxil is a prodrug of adefovir (see abstract)

and mentions that both adefovir as well adefovir dipivoxil are active against hepatitis B virus (see abstract).

- b). On the contrary, the subject-matter of claims 1-9,11, and 19-21 is novel and involves also an inventive step, since the claimed synergistic ratio of lamivudine to adefovir or adefovir dipivoxil has neither been disclosed nor rendered obvious in the available prior art.
- c). Claims should be defined by technical features (Rule 6.3 PCT). In the case of claim 22 information to the patient does not appear to be a technical feature and hence the subject-matter of said claim discloses nothing more than a pack comprising either lamivudine or adefovir dipivoxil (.. "at least one"..). As far as lamivudine is commercially available (Epivir R) the subject-matter of claim 22 is not novel and a claim directed to a patient pack comprising either lamivudine or adefovir dipivoxil characterised by an insert comprising patient information would be not clear (see above).

25 August 2000

**PU3514-PCT** 

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#### Claims

- 1. A combination comprising (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one or a pharmaceutically acceptable derivative thereof and a second therapeutic agent, bis(pivaloyloxymethyl)(9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof wherein (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one and the second therapeutic agent are present in the range 40:1 to 1:1 by weight.
- 2. A combination according to claim 1 wherein the ratio is in the range 25:1 to 15:1 by weight of active ingredients.
- 3. A combination according to any one of claims 1 to 3 for use in medicine.
  - 4. A pharmaceutical formulation comprising a combination according to any one of claims 1 to 3 in association with one or more pharmaceutically acceptable carriers therefor.
  - 5. A pharmaceutical formulation for use in the treatement of HBV comprising (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one or a pharmaceutically acceptable derivative thereof and a second therapeutic agent selected from (9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof, and bis(pivaloyloxymethyl)(9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof wherein (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one and the second therapeutic agent are present in the range 40:1 to 1:1 by weight.
  - 6. A formulation according to claims 4 or 5 in unit dosage form.
  - 7. A formulation according to any one of claims 4 to 6 suitable for oral administration.

25 August 2000

PU3514-PCT

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- 8. A formulation according to any one of claims 5 to 7 comprising between 25 to 150 mg of lamivudine and 5 to 60 mg adefovir dipivoxil.
- 9. A formulation according to claim 8 comprising 100 mg of lamivudine and 10 mg adefovir dipivoxil.
  - 10. A method for the treatment of a mammal, including a human, with an HBV infection comprising administration of a therapeutically effective amount of a combination comprising (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one or a pharmaceutically acceptable derivative thereof and a second therapeutic agent selected from (9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof, and bis(pivaloyloxymethyl)(9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof.
- 11. A method as claimed in claim 10 wherein the combination is as claimed in any of claims 1 to 3.
- 12. A method according to claim 10 or claim 11 wherein the combination is administered simultaneously.
  - 13. A method according to claim 10 or claim 11 wherein the combination is administered sequentially.
- 25 14. A method according to claim 10 or claim 11 wherein the combination is administered as a single combined formulation.
  - 15. A method as claimed in any one of claims 10 to 14 for the treatment of an HBV infection resistant to nucleoside and/or non-nucleoside inhibitors of the replication of the hepatitis B virus
  - 16. Use of (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one in the manufacture of a medicament for administration either simultaneously or sequentially with bis(pivaloyloxymethyl)(9-[2-(phosphonomethoxy)ethyl]adenine, for the treatment of an HBV infection.

PU3514-PCT

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25 August 2000

- 17. Use of bis(pivaloyloxymethyl)(9-[2-(phosphonomethoxy)ethyl]adenine in the manufacture of a medicament for administration either simultaneously or sequentially with (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one for the treatment of an HBV infection.
- 18. Use of a combination comprising (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one or a pharmaceutically acceptable derivative thereof and a second therapeutic agent bis(pivaloyloxymethyl)(9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof for the treatment of an HBV infection.
- 19. Use of a combination as claimed in any one of claims 1 to 3 for the treatment of an HBV infection.
  - Use of a combination comprising (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiclan-5-yl)-pyrimidin-2-one or a pharmaceutically acceptable derivative thereof and a second therapeutic agent selected from either (9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof, or bis(pivaloyloxymethyl)(9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof wherein (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiclan-5-yl)-pyrimidin-2-one and the second therapeutic agent are present in the range 40:1 to 1:1 by weight, for the treatment of an HBV infection resistant to nucleoside and/or nonnucleoside inhibitor.
  - 21. Use of a combination as claimed in any one of claims 1 to 3 for the treatment of an HBV infection resistant to nucleoside and/or nonnucleoside inhibitor of the replication of the hepatitis B virus.
  - 22. A patient pack comprising of at least one active ingredient selected from (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one, and bis(pivaloyloxymethyl)(9-[2-(phosphonomethoxy)ethyl]adenine and an information insert containing directions on the use of both active ingredients together in combination.

**PCT** 

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# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file	reference								
PU3514/PCT	FOR FURTHER ACTIO	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)							
International application	No. International filing date (day/mo	onth/year) Priority date (day/month/year)							
PCT/EP99/06886	17/09/1999	18/09/1998							
International Patent Clas A61K31/00  Applicant	Applicant								
GLAXO GROUP LI	MITED et al.								
	<ol> <li>This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</li> </ol>								
2. This REPORT co	ensists of a total of 5 sheets, including this cove	r sheet.							
been amend		f the description, claims and/or drawings which have as containing rectifications made before this Authority actions under the PCT).							
These annexes c	consist of a total of 3 sheets.								
3. This report conta	ins indications relating to the following items:								
I ⊠ Basis	s of the report								
II □ Priori									
III ⊠ Non-	establishment of opinion with regard to novelty,	inventive step and industrial applicability							
	of unity of invention	, , , , ,							
	soned statement under Article 35(2) with regard ons and explanations suporting such statement	to novelty, inventive step or industrial applicability;							
VI □ Certa	ain documents cited								
VII 🗆 Certa	ain defects in the international application								
VIII □ Certa	VIII ☐ Certain observations on the international application								
Date of submission of the	e demand Date	of completion of this report							
21/03/2000	09.1	0.2000							
Name and mailing addre preliminary examining au		orized officer							
D-80298 M Tel. +49 89	2399 - 0 Tx: 523656 epmu d	nomou, D phone No. +49 89 2399 8599							

International application No. PCT/EP99/06886

### I. Basis of the r port

١.	Das	is of the report							
1.	This report has been drawn on the basis of (substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.):								
	Des	scription, pages:						•	
	1-23	3	as originally filed						
	Cla	ims, No.:							
	1-22	2	as received on	25	5/08/2000	with letter of	25/08/2000		
	Dra	wings, No.:							
	1		as originally filed						
2.	The	amendments have	e resulted in the cance	ellation of:					
		the description,	pages:						
		the claims,	Nos.:						
		the drawings,	sheets:						
3.			een established as if (s beyond the disclosure			ts had not been n	nade, since they have t	peen	
4.	Ado	litional observations	s, if necessary:						
111.	Nor	n-establishment of	f opinion with regard	i to novelty, i	inventive s	step and industri	ial applicability		
			e claimed invention ap able have not been ex			olve an inventive	step (to be non-obvio	ıs),	
		the entire internati	ional application.						
	×	claims Nos 10-15	. 18-21						

because:

Claims 1-9,16-17,22 (YES; see separate sheet, item 2a); 10-15, 18-21

(see separate sheet, items 1 and 2b)



×	the said international application, or the said claims Nos. 10-15,18-21 (see separate sheet, item 1) relate to the following subject matter which does not require an international preliminary examination ( <i>specify</i> ):					
	see separate sheet					
	the description, claims or drawings (indicate particular elements below) or said claims Nos. are so uncleat that no meaningful opinion could be formed (specify):					
	□ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.					
	no international search report has been established for the said claims Nos					
R asoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement						
Statement						
Nov	elty (N)	Yes: No:	Claims Claims	1-21 (see separate sheet, items 3a and 3b) 22 (see separate sheet, item 3c)		
Inventive step (IS)		Yes: No:		1-9,11,19-21 (see separate sheet, item 3b) 10,12-18 (see separate sheet, item 3a)		

2. Citations and explanations

Industrial applicability (IA)

Yes:

No:

Claims

s e separate sheet

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1.

# The following IPER is based on the assumption that the present application is fully entitled to its priority date as claimed.

- 1). Claims 10-15 and 18-21 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).
- 2). a). The subject-matter of claims 1-9, 16-17 and 22 fulfils the requirements of industrial applicability.
  - b). For the assessment of the present claims 10-15 and 18-21 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.
- a). SHAW, T. ET AL: "Synergistic inhibition of in vitro hepadnaviral replication by 3). PMEA and penciclovir or lamivudine." ANTIVIRAL RESEARCH, (1997) VOL. 34, NO. 2, PP. A51. MEETING INFO.: MEETING OF THE INTERNATIONAL SOCIETY FOR ANTIVIRAL RESEARCH AND THE TENTH INTERNATIONAL CONFERENCE ON ANTIVIRAL RESEARCH ATLANTA, GEORGIA, USA APRIL 6-11, 1997 (=D1) discloses synergistic action of a combination of PMEA with lamivudine in ratios of 3:1 and 44:1 (see abstract). In the light of D1, the subjectmatter of claims 10,12-15, although formally novel since it relates to a treatment of a mammal, does not involve an inventive step since the synergistic action of PMEA with lamivudine is obvious from **D1**.

The same applies also to the subject-matter of claims 16-18 defining combinations of lamivudine with adefovir dipivoxil, since it is known from a further document D2 (=MULATO, A.S. ET AL: "Anti-HIV activity of adefovir (PMEA) and PMPA in combination with antiretroviral compounds: in vitro analyses" ANTIVIRAL RES. (1997), 36(2), 91-97) that adefovir dipivoxil is a prodrug of adefovir (see abstract)

International application No. PCT/EP99/06886

and mentions that both adefovir as well adefovir dipivoxil are active against hepatitis B virus (see abstract).

- b). On the contrary, the subject-matter of claims 1-9,11, and 19-21 is novel and involves also an inventive step, since the claimed synergistic ratio of lamivudine to adefovir or adefovir dipivoxil has neither been disclosed nor rendered obvious in the available prior art.
- c). Claims should be defined by technical features (Rule 6.3 PCT). In the case of claim 22 information to the patient does not appear to be a technical feature and hence the subject-matter of said claim discloses nothing more than a pack comprising either lamivudine or adefovir dipivoxil (.. "at least one"..). As far as lamivudine is commercially available (Epivir R) the subject-matter of claim 22 is not novel and a claim directed to a patient pack comprising either lamivudine or adefovir dipivoxil characterised by an insert comprising patient information would be not clear (see above).



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### Claims

- A combination comprising (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-1. oxathiolan-5-yl)-pyrimidin-2-one or a pharmaceutically acceptable derivative selected from (9-I(R)-2second therapeutic agent thereof and (phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof, and bis(pivaloyloxymethyl)(9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof wherein (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one and the second therapeutic agent are present in the range 40:1 to 1:1 by weight.
- 2. A combination according to claim 1 wherein the ratio is in the range 25:1 to 15:1 by weight of active ingredients.
- 15 3. A combination according to claim 1 or 2 wherein the second therapeutic agent is bis(pivaloyloxymethyl)(9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof.
- 20 4. A combination according to any one of claims 1 to 3 for use in medicine.
  - 5. A pharmaceutical formulation comprising a combination according to any one of claims 1 to 3 in association with one or more pharmaceutically acceptable carriers therefor.
    - 6. A formulation according to claim 5 in unit dosage form.
  - 7. A formulation according to any one of claims 5 to 6 suitable for oral administration.
    - 8. A formulation according to any one of claims 5 to 7 comprising between 25 to 150 mg of lamivudine and 5 to 60 mg adefovir dipivoxil.

- 9. A formulation according to claim 8 comprising 100 mg of lamivudine and 10 mg adefovir dipivoxil.
- 10. A method for the treatment of a mammal, including a human, with an HBV infection comprising administration of a therapeutically effective amount of a combination comprising (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one or a pharmaceutically acceptable derivative thereof and a second therapeutic agent selected from (9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof, and bis(pivaloyloxymethyl)(9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof.

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- 11. A method as claimed in claim 10 wherein the combination is as claimed in any of claims 1 to 3.
- 12. A method according to claim 10 or claim 11 wherein the combination is administered simultaneously.
- 13. A method according to claim 10 or claim 11 wherein the combination is20 administered sequentially.
  - 14. A method according to claim 10 or claim 11 wherein the combination is administered as a single combined formulation.
- 25 15. A method as claimed in any one of claims 10 to 14 for the treatment of an HBV infection resistant to nucleoside and/or non-nucleoside inhibitors of the replication of the hepatitis B virus
- 16. Use of (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)30 pyrimidin-2-one in the manufacture of a medicament for administration either simultaneously or sequentially with bis(pivaloyloxymethyl)(9-[2-(phosphonomethoxy)ethyl]adenine, for the treatment of an HBV infection.
- 17. Use of bis(pivaloyloxymethyl)(9-[2-(phosphonomethoxy)ethyl]adenine in the manufacture of a medicament for administration either simultaneously or

WO 00/16755 PCT/EP99/06886

sequentially with (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one for the treatment of an HBV infection.

- 18. Use of a combination comprising (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one or a pharmaceutically acceptable derivative thereof and a second therapeutic agent selected from (9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof, and bis(pivaloyloxymethyl)(9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof for the treatment of an HBV infection.
  - 19. Use of a combination as claimed in any one of claims 1 to 3 for the treatment of an HBV infection.

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- 20. Use of a combination comprising (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one or a pharmaceutically acceptable derivative thereof and a second therapeutic agent selected from either (9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof, or bis(pivaloyloxymethyl)(9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof for the treatment of an HBV infection resistant to nucleoside and/or nonnucleoside inhibitor.
- 21. Use of a combination as claimed in any one of claims 1 to 3 for the treatment of an HBV infection resistant to nucleoside and/or nonnucleoside inhibitor of the replication of the hepatitis B virus.
  - 22. A patient pack comprising of at least one active ingredient selected from (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one, and bis(pivaloyloxymethyl)(9-[2-(phosphonomethoxy)ethyl]adenine and an information insert containing directions on the use of both active ingredients together in combination.

# PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY	PCT				
To: GLAXO WELLCOME PLC Glaxo Wellcome House Attn. Teuten, Andrew J. Berkeley Avenue Greenford Middlesex UB6 ONN UNITED KINGDOM	NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION (PCT Rule 44.1)				
	Date of mailing (day/month/year) 27/03/2000				
Applicant's or agent's file reference PU3514/PCT	FOR FURTHER ACTION See paragraphs 1 and 4 below				
International application No. PCT/EP 99/ 06886	International filing date (day/month/year) 17/09/1999				
Applicant GLAXO GROUP LIMITED et al.	•				
1. X The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.  Filing of amendments and statement under Article 19:  The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):  When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.  Where? Directly to the International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Faschmille No.: (41–22) 740,14,35					
2. The applicant is hereby notified that no international Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.					
3. With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:  the protest together with the decision thereon has been transmitted to the international Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.  no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.					
4. Further action(s): The applicant is reminded of the following:					
Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the international Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.					
Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).  Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority dat or could not be elected because they are not bound by Chapter II.					
Name and mailing address of the international Searching Authority  European Patent Office, P.B. 5818 Patentiaan 2  NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Facc (+31-70) 340-3016  Authorized officer  Claudia Aragone					

Express Mail Lobel EL395942155U3 These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

#### **INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19**

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international policiation. Furthermore, it should be emphasized that provisional protection is available in some States only.

#### What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

#### When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

#### Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 45.2).

Where a demand for international preliminary examination has been his filed, see below.

#### How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

#### What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood, that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

# The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

- [Where originally there were 48 claims and after amendment of some claims there are 51]:
   "Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
- [Where originally there were 15 claims and after amendment of all claims there are 11]: "Claims 1 to 15 replaced by amended claims 1 to 11."
- [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
   "Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or "Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
- 4. [Where various kinds of amendments are made]: "Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

#### "Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

#### Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

#### Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

### PATENT COOPERATION TREATY

# **PCT**

### INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference  FOR FURTHER see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.					
International application No.	International filing date (day/month/year)	(Earliest) Priority Date (day/month/year)			
PCT/EP 99/06886	17/09/1999	18/09/1998			
Applicant GLAXO GROUP LIMITED et al.					
This international Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the international Bureau.  This international Search Report consists of a total of4 sheets.					
X It is also accompanied by	a copy of each prior art document cited in this	report			
1. Basis of the report					
<ul> <li>With regard to the language, the language in which it was filed, uni</li> </ul>	international search was carried out on the bas ess otherwise indicated under this item.	sis of the International application in the			
the International search w Authority (Rule 23.1(b)).	as carried out on the basis of a translation of the	he international application furnished to this			
b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:    contained in the international application in written form.   filed together with the international application in computer readable form.   furnished subsequently to this Authority in written form.   turnished subsequently to this Authority in computer readable form.   the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.   the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.   Certain claims were found unsearchable (See Box I).   Unity of invention is lacking (see Box II).					
4. With regard to the title,  the text is approved as submitted by the applicant.  X the text has been established by this Authority to read as follows:  ANTIVIRAL COMBINATIONS OF LAMIVUDINE AND ADEFOVIR					
5. With regard to the abstract,  X the text is approved as submitted by the applicant.  the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.					
6. The figure of the drawings to be put	lished with the abstract is Figure No.	1			
as suggested by the app		None of the figures.			
because the applicant fair	led to suggest a figure. r characterizes the invention.				
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Form PCT/ISA/210 (first sheet) (July 1998)

International Application No PCT/FP 99/06886

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category °	Citation of document, with indication, where appropriate, of t	he relevant passages	Relevant to claim No.
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<b>1,</b> F	for patients co-infected with		1-21
	HIV AND HEPATITIS.COM, 'Online	)!	
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	ent defining the general state of the art which is not lered to be of particular relevance	or priority date and not in conflict with cited to understand the principle or the	
E" earlier	document but published on or after the International	invention "X" document of particular relevance; the c	
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	ent referring to an oral disclosure, use, exhibition or means	document is combined with one or mo ments, such combination being obviou	re other such docu-
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	actual completion of the international search	Date of mailing of the international sec	
1	.3 March 2000	27/03/2000	
	mailing address of the ISA	Authorized officer	
WILLS COLUM	European Patent Office, P.B. 5818 Patentiaan 2	- Augmice officer	
	NL - 2280 HV Rijewijk Tel. (+31-70) 340-2040, Tx. 31 651 epo ni,	Gonzalez Ramon, N	
	Fax: (+31-70) 340-3016	dollegier ramoli, R	

Form PCT/ISA/210 (second sheet) (July 1992):

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International Application No PCTEP 99/06886

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	<u> </u>	ation) DOCUMENTS CONSIDER BE RELEVANT		
	Category *	Citation of document, with indication, where appropriate, of the relevant passages		Relevant to claim No.
¥	X	SHAW, T. ET AL: "Synergistic inhibition of in vitro hepadnaviral replication by PMEA and penciclovir or lamivudine." ANTIVIRAL RESEARCH, (1997) VOL. 34, NO. 2, PP. A51. MEETING INFO.: MEETING OF THE INTERNATIONAL SOCIETY FOR ANTIVIRAL RESEARCH AND THE TENTH INTERNATIONAL CONFERENCE ON ANTIVIRAL RESEARCH ATLANTA, GEORGIA, USA APRIL 6-11, 1997, XP000890096 abstract		1–21
CA	P,X	DE CLERCQ E: "Perspectives for the treatment of hepatitis B virus infections."  INTERNATIONAL JOURNAL OF ANTIMICROBIAL AGENTS, (1999 JUL) 12 (2) 81-95. REF: 72, XP000890077 abstract; figure 3 page 92, column 2		1–21
IH.	P,X	PESSOA M.G. ET AL: "Update on clinical trials in the treatment of hepatitis B." JOURNAL OF GASTROENTEROLOGY AND HEPATOLOGY, (1999) 14/SUPPL. (S6-S11)., XP000890090 abstract page S10, column 2	·	1–21-
CI	Τ .	PETERS M G ET AL: "Fulminant hepatic failure resulting from lamivudine -resistant hepatitis B virus in a renal transplant recipient: durable response after orthotopic liver transplantation on adefovir dipivoxil and hepatitis B immune globulin."  TRANSPLANTATION, (1999 DEC 27) 68 (12) 1912-4., XP000890081 abstract; table 1		1–21
BA	E	WO 99 66936 A (NOVIRIO PHARMACEUTICALS LIMITE; BRYANT MARTIN L; MYERS MAUREEN W () 29 December 1999 (1999-12-29) claims 11,12,38		1-22
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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

Information on patent family members

International Application No EP 99/06886

Patent document cited in search report Publication date

Patent family member(s)

Publication date

WO 9966936

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29-12-1999

NONE



(PCT Artici 18 and Rules 43 and 44)

pplicant's or agent's file reference  FOR FURTHER see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, Item 5 below.					
International application No.	international filing date (de	y/month/year)	(Earliest) Priority I	Date (day/month/year)	
PCT/EP 99/06886	17/09/1999		18/09/1998		
Applicant GLAXO GROUP LIMITED et al	•				
This international Search Report has been according to Article 18. A copy is being to	n prepared by this internation	nai Searching Auth I Bureau.	ority and is transmitt	ted to the applicant	
	of a total of4 a copy of each prior art doc	sheets. ument cited in this	report.		
Basis of the report     a. With regard to the language, the	International search was car	ried out on the bas	ils of the Internationa	d application in the	
Authority (Rule 23.1(b)).	vas carried out on the basis o	of a translation of th			
was carried out on the basis of the	<ul> <li>With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:</li> <li>contained in the international application in written form.</li> </ul>				
	mational application in com		1.		
	this Authority in written form				
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	bsequently furnished written is filed has been furnished.	sequence listing de	oes not go beyond th	ne disclosure in the	
the statement that the info furnished	ormation recorded in comput	er readable form is	identical to the writt	en sequence listing has been	
	nd unsearchable (See Box	1).			
3. Unity of invention is lac	king (see Box II).			•	
4. With regard to the title,					
the text is approved as su	ibmitted by the applicant.				
The text has been establis					
ANTIVIRAL COMBINATIONS OF LAMIVUDINE AND ADEFOVIR					
5. With regard to the abstract,					
the text is approved as su	ibmitted by the applicant.				
the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.					
6. The figure of the drawings to be publ	ished with the abstract is Fig	jure No.	1		
as suggested by the appli	cant.			None of the figures.	
X because the applicant fall	ed to suggest a figure.				
because this figure better characterizes the invention.					